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A Simpler Route for Making Nitrogen-Alkene Rings

A common nitrogen building block used in many natural product and drug syntheses can now be made in its unprotected form in a single step..

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Nitrogen is a key component of many natural products and drug molecules. It has been estimated that among all natural products, the average number of nitrogen atoms per molecule is 0.7, while for medicinal drugs, this number rises to 3.0 (*1*). A versatile method for the synthesis of nitrogen-containing molecules is to use nitrogen-bridged alkenes (aziridines) as building blocks, as the ring strain makes them highly reactive. Aziridines are also present in a number of biologically active natural products (*2*) (see the figure, panel A). Current aziridination methods (*3*-*5*) almost always require the use of a protecting group, on the nitrogen atom. The removal of these groups can sometimes be problematic because of the need for harsh reaction conditions. A direct aziridination method that would circumvent the need to use such a protecting group has so far remained elusive with few exceptions (*6*-*8*). Thus, practical and direct methods for the preparation of aziridines are very useful. On page xx of this issue, Jat *et al.* (*9*) report the direct synthesis of *N*-H and *N*-Me aziridines in a single step and under mild reaction conditions.

In the aziridination method developed by Jat *et al.*, the reaction of an alkene—a functional group that contains a C-C double bond—with the aminating agents DPH or *N*-Me-DPH [where DPH is *O*-(2,4-dinitrophenyl)hydroxylamine and *N*-Me denotes adding a methyl group onto the amine] in the presence of a rhodium catalyst affords *N*-H or *N*-Me aziridines at ambient temperature (see the figure, panel B). The success of this methodology lies in the identification of the correct combination of aminating agent, rhodium catalyst, and solvent. The initial reaction of DPH with the rhodium catalyst is proposed to give a transient rhodium nitrene, a reactive intermediate with a double bond between the nitrogen and rhodium. This species is electrophilic and reacts with nucleophiles, in much the same way as opposite poles of a magnet are attracted to each other. In the reaction mixture are alkenes and DPH, both of which are nucleophiles, but the transient rhodium nitrene intermediate reacts selectively with the alkene reactant, resulting in the successful formation of the aziridine product.

In previous work, related aminating agents (e.g., PhINTs, TsNClNa, where Ph is phenyl and Ts is tosyl) were rendered nonnucleophilic by adding a protecting group. Such groups not only add extra steps in a synthesis, but they can also be difficult to remove from the final product. Through screening different catalysts, reagents, and solvents (the solvent trifluoroethanol was crucial) Jat *et al.* discovered a new, high yielding aziridination process. Not only did the process use a low loading of catalyst, which makes it more efficient, but it also showed very broad substrate scope and high functional-group tolerance. Furthermore, the reaction preserves the two-dimensional arrangement of the groups of the starting alkene in the three-dimensional arrangement of the groups on the aziridine product. Additionally, the feasibility of ring opening reactions of the *N*-H aziridine products was demonstrated in three examples affording the primary amine products in high yields (see the figure, panel B).

The new method developed by Jat *et al.* is expected to find widespread use in synthetic organic chemistry. The aziridine products can be activated for ring-opening reactions by various Brønsted acids, Lewis acids, or other groups that are directly required in the final products (e.g., amides). This flexibility will minimize the need for functional group manipulations and hence increase the efficiency of a synthetic sequence. Furthermore, most aziridines found in the natural products are generally in their *N*-H or *N*-Me forms, and the new aziridination protocol has the potential for synthesizing these natural products directly, without the need for deprotection of this sensitive and reactive functional group.

Many biologically active, nitrogen-containing molecules are present in single mirror-image forms (enantiomers), and because the two forms show different biological activity, it is highly desirable to make one of the two forms selectively. Otherwise, they must be separated after synthesis. A major challenge regarding the method developed by Jat *et al.* is whether it can be rendered asymmetric by the use of a chiral catalyst, as this capability would then make the methodology even more attractive.

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Following an unprotected route. (**A**) Examples of biologically active, aziridine-containing natural products are shown. (**B**) The reaction of alkenes with the aminating reagent DPH in the presence of a rhodium catalyst was shown by Jat *et al*. to afford *N*-H aziridines in a single step. Primary amines were obtained in high yields by the ring-opening reactions of the aziridine products.